WHY DO MEDI

By T. Lauder Brun

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WHY DO MEDICINES SOMETIMES FAIL TO ACT?

By T. Lauder Brunton, M.D., F.R.S., and J. Theodore Cash, M.D.

(Reprinted from *St. Bartholomew's Hospital Reports*, 1885, vol. xx.)

Of late years the systematic investigation of the action of drugs in physiological laboratories has been greatly extended, and has yielded very useful results, most of the important drugs recently added to our materia medica having been introduced into medical practice in consequence of their physiological action having been first ascertained by experiment upon animals. But when we come to administer drugs to patients suffering from disease, we are not unfrequently disappointed in the results we obtain, not only from new medicines of recent introduction, but from those which have been in use for centuries, and whose reputation has been thoroughly established.

These failures are apt to induce some persons to regard therapeutics as a subject essentially uncertain in its nature, and to relinquish any hope of ever obtaining a definite knowledge of the action of medicines in disease. If we consider the subject a little more carefully, however, we shall readily see that therapeutics is no more uncertain than chemistry, although the conditions under which a reaction occurs between the medicine administered and the body of a patient on a sick bed, are more complicated than those under which reaction occurs between two chemicals in the laboratory.

So long as we deal exclusively with complex conditions, we cannot hope to ascertain the action of drugs in disease with any amount of certainty. The object for which we must strive is to study the action of medicines under various conditions, so that when we administer them to our patients we shall be certain of effecting the purpose we desire. We must not confine our experiments to animals in a normal condition; we

must try to analyse the circumstances under which drugs are to act when given to a patient; and by testing the effect of these conditions one by one upon animals, we may hope at length to obtain a definite knowledge of the effect of drugs in disease.

One of the most important conditions influencing both chemical and pharmacological reactions is temperature. Thus the substances which compose gunpowder, however intimately they be mixed together, show no tendency to unite chemically at ordinary temperatures, but at a sufficiently high temperature they combine with explosive violence. The first step in the making of such drugs as corrosive sublimate or calomel is to prepare sulphate of mercury; and though sulphuric acid does not attack mercury at ordinary temperatures, yet it does so when heated, forming a salt. Nitric acid attacks mercury and forms a nitrate at ordinary temperatures; when heated, this salt is decomposed, nitrous fumes being given off, and red oxide remaining behind; as the temperature is raised, the oxide itself is decomposed into oxygen and metallic mercury. In such processes as these the effect of temperature upon the behaviour of chemical substances is clearly marked. Its influence is, we think, no less distinct upon the reaction between drugs and animal tissues or organs, although the range through which the temperature can vary without destroying the vitality of the tissues is much more limited than in the case of inorganic substances.

A good example of the effect of temperature in modifying the reaction between a drug and an animal tissue is afforded by the behaviour of a muscle poisoned by veratria.

Veratria curve.

FIG. 1.—Contraction of Frog's gastrocnemius poisoned by veratria. Stimulation by a single induction shock. Temperature 25° C.

The effect of this poison upon muscle at ordinary temperatures is to strengthen its contractile power, and to prevent the ready relaxation by which the contraction is succeeded in the normal muscle. The consequence of this is that a frog poisoned with this substance can spring as well or better than a normal one; but after the spring is over, instead of the legs being drawn up close to the body ready for action again, they remain stiff and extended. The extensor muscles, instead of relaxing after their work is done, remain contracted, so that the flexor muscles are unable to act. After a while the rigidity passes off, and the legs are drawn up close to the body; but now the flexor muscles, having been used, remain in a contracted condition, and the animal is unable to spring again until the spasm of the flexors has passed off.

There are very few such striking examples of the action of a drug upon an animal as that of veratria. But this effect is one that occurs only at ordinary temperatures. If the poisoned muscle be cooled down, the veratria effect is diminished, and may disappear altogether; the same is the case when the temperature is considerably raised. This is seen by an examination

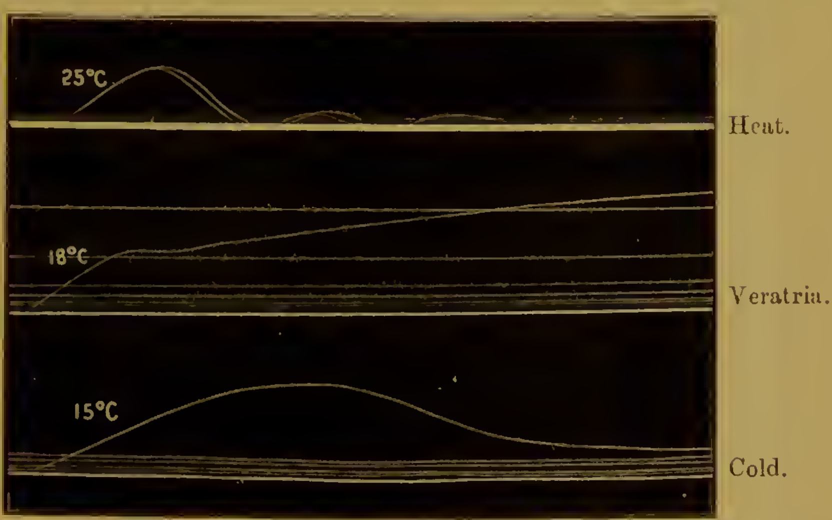


FIG. 2.—The lowest muscle curve is taken from a veratria muscle cooled to 15° C. The middle curve is taken from the same muscle at room temperature; the uppermost curves from the same muscle heated to 25° C.

of the accompanying curves, which appeared in a paper we have previously published.*

The salts of barium, applied locally to frog's muscle, have an action closely resembling, though not identical with, that of veratria. They frequently cause a very similar alteration in the muscular contraction, and this is removed, like that of veratria, by exposure to heat or cold. The variations in temperature which are requisite to destroy the action of barium upon muscle are much greater than could possibly occur in the mammalian body.

At the same time it must be remembered that the doses with which we experimented were enormously greater than those which would be used in medicine. It seems not improbable that the effect of a very small dose might be removed by a much less extensive alteration in temperature. Neglect of the temperature at which experiments have been made is one cause of the contradictory results which have frequently been obtained in the investigation of the action of different drugs. Thus atropine was found by Bowditch and Luciani to increase the systolic contraction of the frog's heart; while Gnauck, on the other hand, obtained an exactly opposite result, and found that both atropine and hyoscyamine diminished ventricular contraction. At Kronecker's suggestion, the research was taken up anew by Schapiro,† who repeated the experiments at different temperatures, and found that both observers were right, and both were wrong. When the experiments were made at a low temperature, 7° to 8° C., atropine amplified the contractions of the heart, as stated by Bowditch and Luciani; but when the temperature rose about 15° C., atropine had an exactly opposite effect, and diminished the contractions, as stated by Gnauck.

The effect of seasons of the year upon the antagonistic action of drugs in the body was observed by Ringer,‡ who found that while pilocarpin antagonises the action of muscarin

* 'On the Action of Heat and Cold on Muscles Poisoned by Veratria,' *Journal of Physiology*, vol. iv, No. 1.

† *Centralblatt f. d. med. Wissenchaft.*, August, 1884, No. 33.

‡ *Journal of Physiology*, vol. iii, p. 115.

and atropine antagonises aconitine upon frogs in summer, it has no such action in winter. Similar observations were made by Pantelejeff* in regard to atropine and quinine.

In summer, quinine arrests the frog's heart in diastole; atropine subsequently administered causes the pulsations of the heart to recommence. In winter, quinine acts much more slowly upon the heart, and atropine increases instead of antagonising its action.

The opinion expressed by various authors, that the action of drugs may be largely varied by climate, has often been received with distrust. There seemed to be no very definite reason for supposing that climate should exercise this action, and so any difference that might exist was apt to be ascribed to other causes. The statement of Lisfranc, that the inhabitants of southern climates tolerate much larger doses of barium than those of northern climates, is at first sight curious, and one may be inclined to be sceptical regarding it. There seems no obvious reason why an inorganic substance like barium should act differently in Italy and in England, although one might be inclined to grant that such a modification might perhaps occur in the case of more complex and less stable organic substances. The marked effect of heat upon voluntary muscle poisoned by barium, however, seems to indicate that the resistance opposed to the action of the drug by inhabitants of warmer countries may be due to the higher temperature, and we have found experimentally that cold retards the fatal effect of barium upon guinea-pigs.

It must be remembered that the temperature of the human body and of that of mammals in general is not absolutely constant, but oscillates up and down, although it is quite true that these oscillations occur within narrow limits. Thus, John Davy found in a transit from a hot to a temperate climate, that when the mean temperature of the air had fallen 20° F., the temperature of the body fell 1·58° F., and Brown-Séquard noticed in eight healthy people a rise of 2° F. in travelling from France with an atmospheric

* *Centralblatt f. d. med. Wissenchaft.*, 1880, p. 529.

temperature of 46·4° F. to the Equator, where the temperature was 85·1° F.*

The temperature of the body also varies with the time of day; the daily maximum, according to most observers, being in the afternoon, and the minimum in the early morning. These daily variations are much less than those already mentioned as occurring from change of climate, and possibly they are too slight to have any marked effect on the action of most medicines; yet, in any attempt to ascertain precisely the causes why the medicines we administer fail at one time and succeed at another in producing the action we desire, we must bear in mind the possibility of their action being altered even by such small factors as diurnal variations in temperature.

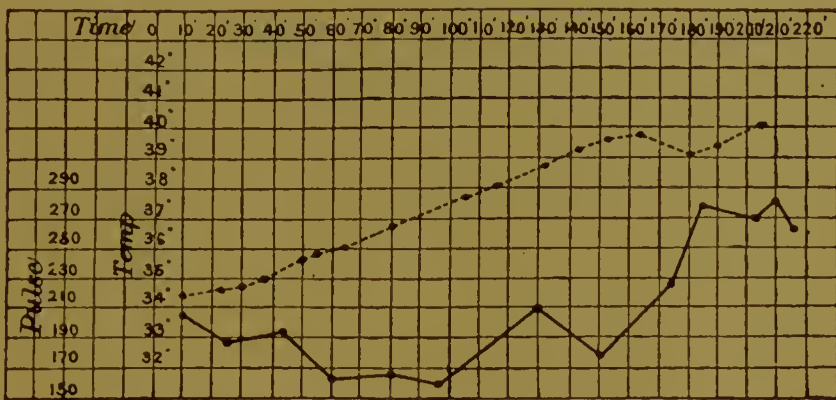
Very remarkable is the effect of temperature on the action of guanidine. This substance at ordinary temperatures, *e.g.*, 18° C. (64·4° F.), produces fibrillary twitchings and convulsions in frogs. At high and low temperatures, however, it has no effect. Thus, if three frogs are poisoned in exactly the same way, and one be placed in iced water but little above 0° C (32° F.), another in water at 18° C. (64·4° F.), and another in water at 32° C. (89·6° F.), the first and third remain unaffected, whilst muscular twitchings and convulsions make their appearance in the second. Another curious point in regard to the action of temperature is that moderate rise of temperature, within certain limits, increases the effect of the drug, although a great rise completely destroys it. Thus, if in addition to the frogs already mentioned, another be poisoned and placed in water at 25° C. (77° F.), the convulsions are more violent than at 18° C., although when the temperature is raised to 32° C. the poison ceases to produce its usual action, and five times the normal dose may be given without doing any harm.†

No doubt febrile temperatures have a great effect in modifying the action of medicines administered for the cure of

* Wunderlich, *Medical Thermometry*, Syd. Soc. ed., p. 114.

† Luchsinger, *Physiologische Studien*, Leipzig, 1882. In a paper which only came into our hands after the completion of this sketch, Hess and Luchsinger (*Pflüger's Archiv*, vol. xxxv, p. 174) state that in the case of rabbits poisoned with chloral, alcohol, mercury, and other substances, great elevation of temperature accelerates, slight elevation retards or diminishes, the action of the drug.

disease. We have studied this point with reference to the action of digitalis upon the cat,* and found that the effect of the drug upon the pulse-rate was either greatly diminished or



The unbroken line shows the pulse-rate, the dotted line shows the temperature in the axilla in all the figures.

Fig. 3.—Shows the effect of rise of temperature alone. At the 195th minute both vagi were cut; the section was not followed immediately by any apparent effect. After eight minutes more, the pulse-rate rose slightly and then fell

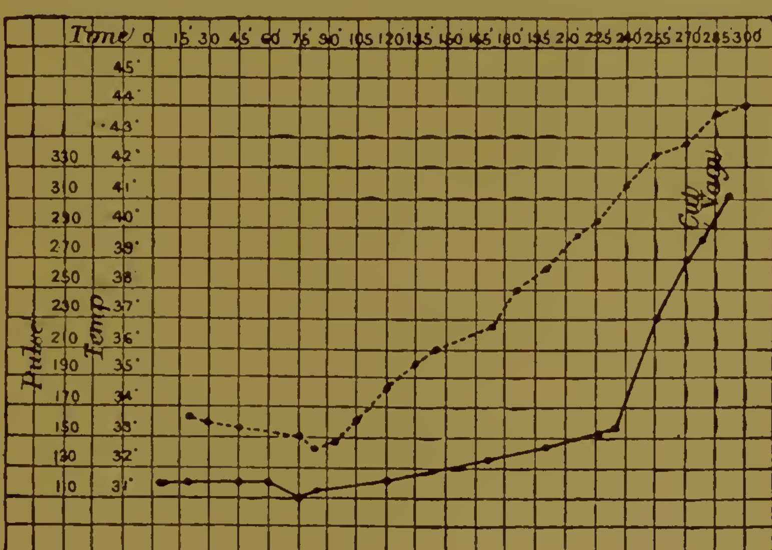


Fig. 4.—Shows the effect of rise of temperature after injection of digitalis. At the 45th minute 0·75 cc. (12 minims) tincture of digitalis were injected, and another similar injection was made at the 55th minute. At the 65th minute the heating was begun.

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* *Practitioner*, October, 1884, p. 272.

completely abolished after the temperature had risen above a certain point.

In the present paper we propose to describe some experiments upon another factor modifying the action of drugs, viz., food. The practical object which we had in view was to ascertain whether the effect of remedies employed in disease might not be very much influenced by the large quantities of beef-tea often administered to patients. Beef-tea is a complex substance and contains many ingredients. Our inquiry regarding it is by no means complete, for in the present paper we deal with only one of its constituents, viz., salts of potassium. These form, however, a very important constituent —so important that Bunge was led by his experiments to regard the action in toxic doses at least as very similar, if not identical.

In a former paper* we have shown that the peculiar effect of barium on voluntary muscle is antagonised by potash; it seemed natural to conclude from this result that potash administered at the same time as barium might antagonise its usual action in the case of warm-blooded animals and prevent death.

	Dose of Barium Chloride.	Dose of Potassium Chloride.	Result.
	Gram.		
1	0·1 per kilo. body-weight	None	Died.
2	0·015 " "	—	Recovered.
	0·05 " "	—	Recovered.
	0·1 " "	—	Died.
3	0·045 " "	None	Died.
4	0·08 " "	None	Died.
5	0·06 " "	KCl 0·075 per kilo.	Recovered.
6	0·05 " "	KCl 0·174 per kilo.	Recovered.
	0·05 " "	None	Died.

From the above table it appears that the lethal dose of chloride of barium is between 0·04 and 0·08 per kilogram body-weight in guinea-pigs. In one case in which potassium chloride was administered with a dose of 0·06 barium chloride,

* *Phil. Trans.*, Pt. 1, 1884, p. 225.

the animal recovered from the immediate effects of the barium; and in a second case where 0·174 per kilogram potassium chloride was administered, a dose of 0·05 per kilogram barium chloride did not kill. On repeating the same dose of barium on the succeeding day by itself, death ensued. These experiments show, we think, that potash does to a certain extent antagonise the usual action of barium. A number of other experiments have also given us indications of antagonism between these substances, but the results were not so definite as in these experiments, death being delayed only two hours, or even less. A much more extended series of experiments would therefore be required to ascertain the precise limits of antagonism.

The action of barium upon guinea-pigs seems to depend to some extent upon individual idiosyncrasy, some animals appearing to be more tolerant of it than others.

Idiosyncrasy is one of the bugbears of therapeutics. It is at present impossible to tell with absolute certainty what effect a drug will produce upon any individual even when it is administered in health, and when its effect is not interfered with by alterations in climate or by disease. We know perfectly well that in ninety-nine cases out of every hundred, or even nine hundred and ninety-nine out of every thousand, certain drugs will have a definite action. Thus five grains of aloes will purge, two grains of quinine or calomel may be given without producing any disagreeable results; but every now and again we meet with individuals whom purgatives, even in enormous doses, will not affect at all, and with others in whom all the symptoms of poisoning by quinine or mercury are produced by such small doses as those just mentioned. We find something analogous to the idiosyncrasies which sometimes cause a variation between two individuals of the same species, in the difference between the effect produced by certain drugs or morbid agencies upon different species or genera of animals. Thus rabbits are apparently little affected by belladonna, whilst dogs are readily affected by it. French sheep and house-mice are readily affected by anthrax, whilst Algerian sheep, rats, and field-mice offer great resistance to it.

It seems to us not improbable that such differences as these may partly depend upon the different chemical composition of each animal, and the different proportions of the various saline constituents of their bodies.

It has been found that, by giving an animal food containing a larger proportion of common salt than usual, the amount of sodium chloride in its body can be increased. When the quantity of salt contained in the food remains nearly the same every day, as much is excreted in the urine as is contained in the food, and thus the quantity in the body remains constant. If a larger quantity be now given with the food, a corresponding rise does not occur in the quantity excreted; the salt becomes stored up in the organism for two or three days, and then the excretion rises, so as to counterbalance the larger consumption; the amount in the body remains constant, but at a higher level—if we may so term it—than before. If the quantity contained in the food be now reduced, a corresponding reduction does not occur in the urine at once; the excess which has been stored up in the body is gradually eliminated, and then, after two or three days, excretion and consumption again counterbalance each other. The amount in the body is again constant, but at a lower level. It occurred to us that we might be able to increase the proportion of potash in the body in a similar manner by giving food containing an excess of potash salts. We thought that if this plan were successful the animal might be rendered less susceptible to the influence of such drugs as are to some extent antagonised by potassium, or perhaps entirely protected from their usual action.

The following experiments show that, although our hopes of entirely counteracting barium by previously feeding animals with potash were not fulfilled, yet such an amount of protection was bestowed, that animals fed with potash remained alive, in many instances, for a longer time than those poisoned with an equivalent dose of barium, but had not been so protected. In one case, after 2·26 potassium chloride (per kilogram of body-weight) had been administered in the course of three days, there was complete recovery after poisoning with 0·05 (per kilogram) barium, the same dose being fatal in an unprotected guinea-pig.

	Dose of Barium Chloride.	Dose of Potassium Chloride.	Result.
1	Gram. 0·066 per kilo. body-weight	Had taken about 3 grms. KCl with food in ten days.	Recovered.
2	0·086 " "	Had taken 1·5 grm. KCl with food in three days.	Recovered temporarily, but died of exhaustion caused by purging from barium.
3	0·086 " "	Had taken 2·5 grms. KCl with food in five days.	Died in 67 minutes.
4	0·100 " "	Had taken 3 grms. KCl with food in eight days.	Living seven hours after administration of barium, but died in course of night.

This result seems to indicate that there may have been some foundation for the old idea that it was possible by the previous use of an antidote to protect the organism to some extent from the effects of the poison. The protection thus afforded, however, appears to be limited, both in regard to the quantity of poison and also its nature. The effect of veratria upon muscles is very similar to barium, and is counteracted in much the same way by potash salts; but the following experiment shows that the usual effect of veratria upon the organism is not counteracted by a considerable quantity of potash. In the guinea-pig we estimate that the lethal dose of veratria is from 0·004 to 0·006 per kilogram body-weight; fatal in about two hours.* One guinea-pig (of 678 grms.) which had received 2·125 grms. potassium chloride in all in five days, died in 80′ after the administration of 0·007 veratria per kilogram body-weight. This is slightly in excess of the usual dose, which lies somewhere about 0·005

* Rossbach, *Handbuch d. Arzneimittellehre*, pp. 756–771. According to Rossbach, the lethal dose of veratria for cats, fatal in about two hours, is 0·005 for one animal. Estimating the weight of a cat at 3 kilograms, the lethal dose per kilogram would be about 0·0016, so that cats are much less tolerant than guinea-pigs.

per kilogram for guinea-pigs. We found, however, that repeated administration of the drug on successive days seemed to develop a tolerance of the animal towards it, so that a dose which would have been fatal in the first instance was recovered from when preceded by smaller doses.

On summing up the results of the experiments upon barium and potash, it is found—

1st. The effect of barium upon muscle is counteracted by potash.

2nd. The effect of barium upon the body is counteracted to some extent by potash administered at the same time.

3rd. The effect of barium upon the body is counteracted within certain limits by potash given in the food for several days previously.

4th. It seems possible that the idiosyncrasies of different species of animal, or of individuals of the same species, both in regard to the action of drugs upon them, and in regard to their susceptibility to infection, may depend on the relative proportion of inorganic salts contained in their bodies.

It is evident that the indications afforded by these experiments open up an immense field of research both in pharmacology and pathology, and one which it would take many years to investigate completely.

We have been able to do little more as yet than to enter the precincts of it, and only one step has been made in ascertaining the effect of beef-tea upon barium salts, viz., of the former upon muscles poisoned with the latter.

From the following curves it is evident that beef-tea removes the effect of barium upon muscles in much the same way that pure salts of potash would do.

At the same time there appears to be a distinct difference between the beef-tea and the potash salts, for the latter quickly reduce the height and duration of the muscle curve below the normal, while beef-tea does not, at least when it is given in similar concentration.

As beef-tea agrees to a certain extent with potash salts in their effect upon muscles poisoned by barium, it is natural to

expect that beef-tea may also modify the action of barium upon the body generally, and perhaps antagonise to a certain extent the usual action of barium. We have not yet been able

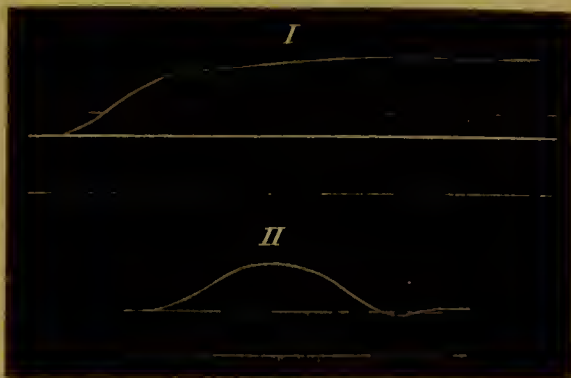

Fig. 5.

I. Curve of gastrocnemius of frog. The muscle has been 20′ in barium chloride solution 1–600.
II. Curve of the same muscle after 30′ in chloride of potassium solution 1–600.

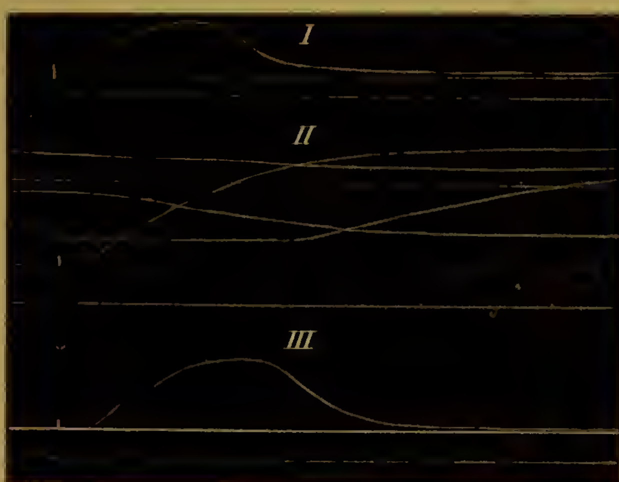

Fig. 6.

I. Curve of gastrocnemius of frog.
II. Curve of the same muscle after immersion for 20′ in barium chloride solution 1–500.
III. Curve of the same muscle after immersion for 20′ in diluted Liebig's extract 1–300.

to test this experimentally by giving beef-tea or meat extract, either along with barium, or mixed with the food for several days previously. Nevertheless, it appears advisable to publish

the results of our experiments as far as they have gone, rather than to wait for their completion, because the inquiry is one which can be conducted at the bedside as well as in the laboratory.

The experiments on the alterations produced by beef-tea or meat extract in the action of barium salts would be, after all, only preliminary to a far more extensive study, even were they complete.

Barium is at present rarely or never prescribed as a medicine, and any alteration in its action which beef-tea or meat extract could produce would be at present only of theoretical interest. But the question is a widely different one when we come to deal with digitalis, convallaria, caffeine, broom, juniper, and other cardiac tonics and diuretics, as well as quinine, salicin, salicylate of soda, and other anti-pyreties.

In cases where these are administered, the patient is not unfrequently very weak and low, so that beef-tea, or a strong solution of Liebig's extract, is often given in considerable quantities for the purpose of maintaining strength. Ringer has already shown* that the effect of veratria on the frog's heart is antagonised by potash salts, and it is possible that when we give large quantities of beef-tea along with cardiac tonics we may thus be undoing with the one hand what we are doing with the other, and neutralising, by the kind of food used, the action of the medicine to which we trust for the patient's recovery.

An extensive series of experiments on animals is still required in order to lessen, so far as possible, unnecessary trials upon patients; yet, at the same time, a large amount of valuable information might be obtained by medical men observing whether digitalis and caffeine, for example, are most successful when the diet consists chiefly of milk and farinaceous food, or whether the addition of beef-tea, or the old-fashioned nutrient wine-whey, interferes with or increases the efficacy of these remedies.

* *Practitioner*, January, 1883, p. 17.

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